# UNITED STATES PATENT AND TRADEMARK OFFICE

## BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DANILO D. LASIC, ROBERT M. ABRA, YECHEZKEL BARENHOLZ, and TAL PELEG-SHULMAN

Appeal No. 2006-2213
Application No. 09/771,151

ON BRIEF



Before ADAMS, GRIMES, and GREEN, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims directed to methods of preparing liposomes containing supersaturated solutions of drug compounds. The examiner has rejected the claims as anticipated. We have jurisdiction under 35 U.S.C. § 134. We affirm.

Background

"Liposomes are completely closed lipid bilayer membranes containing an entrapped aqueous volume." Specification, page 1. "A primary use of liposomes is to serve as carriers for a variety of materials, such as, drugs, cosmetics, diagnostic reagents, bioactive compounds, and the like." Id. "[L]oading of uncharged and non-lipophilic drugs [into liposomes], and in particular drugs having low solubility in aqueous

phase at a sufficiently high drug-to-lipid ratio for efficacious therapy remains a problematic issue." Page 2. The specification discloses that one may obtain a liposome having an increased drug to lipid ratio by entrapping a supersaturated solution of a drug within the liposome. Page 3.

To prepare a supersaturated solution of a drug compound, one must first select a compound whose solubility can be increased at least two-fold over its room temperature solubility. Page 6. The compound's solubility can be increased by, e.g., raising the temperature of the solvent, adding a co-solvent, or changing the pH of the solvent. Id. The specification discloses that the anticancer drug cisplatin is suitable for use in preparing supersaturated solutions because it is much more soluble at elevated temperatures than at room temperature. Id. Thus, for example, a supersaturated solution of cisplatin can be obtained by heating a solution containing cisplatin at a concentration greater than its room temperature solubility limit. Pages 6-7.

To entrap the supersaturated solution within liposomes, a separately prepared lipid composition is hydrated with the supersaturated solution of the drug. Page 7. The specification discloses that the lipid preparation may contain lipids which are derivatized with polymers such as polyethylene glycol. Id.

The resulting liposomes containing entrapped supersaturated solutions of drug compounds can be prepared in desired sizes by known methods including sonication, homogenization or extrusion. Page 8. The specification discloses that by adjusting the size of the liposomes appropriately, one can inhibit precipitation of the drug from the entrapped supersaturated solution, even under conditions in which the drug would normally precipitate. Id.

Thus, for example, when a supersaturated solution of a drug is prepared by heating the solution to increase drug solubility, the temperature can be lowered once the supersaturated solution is entrapped within a liposome preparation. Id. If the liposomes are of the correct size, the drug will not precipitate, even at a temperature that would not normally support a supersaturated solution. Id. To ascertain whether the drug within the liposome has precipitated, one may use spectroscopic techniques or visual methods such as microscopy. Id. The specification discloses that liposome sizes preferred for maintaining supersaturated solutions range from about 70-500 nm, with liposomes of about 60-1,000 nm being "suitable." Id.

## Discussion

### 1. Claim construction

Claims 1, 3-9, and 16 are pending and stand rejected.

Appellants' argument focuses entirely on whether the prior art describes elements within claims 1 and 16, the appealed independent claims.[1] We will therefore focus on claims 1 and 16, which read as follows:

> 1. A method for preparing liposomes having an entrapped compound in the form of a supersaturated solution, comprising:
>
> selecting a compound having room temperature water solubility capable of exhibiting at least a two-fold increase in response to a condition selected from the group consisting of: (i) increasing solvent temperature, (ii) adding a co-solvent, and (iii) changing solvent pH;
>
> preparing from a supersaturated solution of the compound liposomes at selected size intervals;
>
> analyzing said liposomes for the presence or absence of precipitated

[1] Page 2 of the Brief inadvertently lists claim 1 as the only independent claim. ("Sole independent claim 1 describes . . . ."). However, claim 16 is also independent.

compound; and

based on said analyzing, selecting liposomes of a size that corresponds to liposomes having no entrapped precipitated compound.

16. A method for preparing liposomes which contain a supersaturated solution of a compound, comprising:

preparing an aqueous supersaturated solution of a compound;

hydrating a lipid film or a lipid solution with said supersaturated solution of the compound to form liposomes;

sizing the liposomes to selected sizes;

analyzing the liposomes at each size for the presence or absence of precipitated compound; and

based on said analyzing, selecting liposomes having a size that corresponds to liposomes having no precipitated compound.

Thus, claims 1 and 16 are directed to methods of preparing liposomes having supersaturated solutions of compounds entrapped within them. Claim 1 requires: (a) selecting a compound showing at least a two-fold solubility increase under specified conditions; (b) preparing liposomes of selected sizes that contain a supersaturated solution of the compound; (c) determining whether the liposomes contain precipitated compound; and (d) "based on the analyzing step," selecting liposomes of a size having no precipitated compound in them.

Claim 16 is similar to claim 1 but differs by (a) not requiring the solubility of the compound to be at least two-fold higher under specified conditions, and (b) requiring that the liposomes be formed by hydrating a lipid film or solution with a supersaturated solution of the compound.

2. Anticipation by Abra

The examiner rejected claims 1, 3-9, and 16, all of the pending claims, under 35 U.S.C. § 102(b) on the basis that the claimed method is anticipated by Abra.[2] The examiner stated that Abra "discloses a method of preparation of liposomes containing supersaturated solution of an active compound. The liposomes further contain a hydrophilic polymer (PEG) (note the abstract, page 2 line 15 through page 3, line 24, page 6, lines 14-26, page 12, lines 4-21, Example 3 and claims)." Answer, page 4.

In response, Appellants argue that "Abra et al. fail to teach selection of liposome size in order to maintain the compound in the form of a supersaturated solution. Specifically, Abra et al. fail to teach each of steps (ii), (iii) and (iv) as set forth in independent claims 1 and 16." Brief, page 8. Appellants urge that Abra's process comprises only the two steps of (a) heating a cisplatin solution to increase the drug's solubility, and (b) producing liposomes from the heated drug solution, and that "[n]owhere does Abra et al. teach steps of 'preparing liposomes at selected size intervals', 'analyzing the liposomes as a function of size for the presence of precipitated compound', or 'based on the analyzing selecting a liposome size that corresponds to liposomes having no precipitated compound' as presently claimed." Id.

Appellants emphasize Abra's explicit statement, at page 4, lines 34-35, that the cisplatin is entrapped within the liposomes "in dissolved form or in precipitated form." Id., at pages 8 and 9. Thus, Appellants urge, "[b]ecause the liposomes of Abra et al. could include the cisplatin drug in precipitated form, it cannot be said that Abra et al. inherently anticipates the claimed process of preparing liposomes with drug solely in the

[2] Abra, WO 98/07409, published February 26, 1998

supersaturated form, or that claim steps (ii), (iii), and (iv) that are undisclosed by Abra et al. are inherent in the document's disclosure." Id., at page 9, emphasis in original.

Patentability determinations are based on a preponderance of the evidence. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) ("After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument.").

As pointed out by Appellants (Brief, page 4), "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). However, discovery of a property inherent to a prior art process does not render that process patentable, even if the prior art did not appreciate the property. Id. at 632-33, 2 USPQ2d at 1054. Thus, "[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1376, 58 USPQ2d 1508, 1514 (Fed. Cir. 2001). Furthermore, "[i]nsufficient prior understanding of the inherent properties of a known composition does not defeat a finding of anticipation." Atlas Powder Co. v. IRECO Inc., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

Based on a preponderance of the evidence, we agree with the examiner that Abra discloses all of the claimed process steps, including the steps of preparing liposomes at selected size intervals, analyzing the liposomes for the presence of

precipitated compound, and selecting a liposome size that corresponds to liposomes having no precipitated compound.[3]

Regarding the claimed step of preparing liposomes at selected sizes, page 12 of Abra (cited in the examiner's rejection) states at lines 13-14, that "[t]he liposomes, following diafiltration and dialysis, were extruded through 0.2 μm and 0.1 μm polycarbonate filters to size the liposomes to between about 100-120 nm." (Emphasis added.) In our view, this disclosure meets the limitation in claims 1 and 16 requiring the preparation of liposomes of selected sizes.

Regarding the claimed step of analyzing the liposomes for the presence or absence of precipitated compound, Abra performed a number of analyses on the liposomes described on page 12. Specifically, Abra determined (page 12, lines 17-18) the concentration of cisplatin within the internal phase of the liposomes. ("The final liposomes contained an internal phase of cisplatin encapsulated at a concentration of 8.5 mg/ml in 0.9% sodium chloride . . . ."). Abra also evaluated the stability of the liposomes (page 12, line 23, through page 14, line 8). The stability analysis required "determining the percent of encapsulated platinum" (page 12, lines 25-26), as well as verifying that the encapsulated platinum was "in the form of cisplatin" (page 13, lines 32-33).

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[3] Regarding Appellants' statement that "Abra et al. fail to teach each of steps (ii), (iii) and (iv) as set forth in independent claims 1 and 16" (Brief, page 8), we note that the second, third, and fourth steps of claim 1 actually correspond, albeit not identically, to the third, fourth and fifth steps of claim 16. Despite Appellants' numbering scheme, however, it is clear from their argument that Appellants assert that Abra does not disclose the claimed steps of preparing liposomes at selected size intervals, analyzing the liposomes for the presence or absence of precipitated compound, and based on the analyzing, selecting a liposome size that corresponds to liposomes having no precipitated compound.

In view of Abra's extensive analysis of the liposomes (pages 12-16), it is reasonable to expect that precipitated cisplatin would have been detected if it had been present. Abra's liposome analysis therefore reasonably appears to be a step of "analyzing . . . liposomes for the presence or absence of precipitated compound," as recited in claim 1.

As pointed out by Appellants, Abra states on page 4, lines 34-35, that "[t]he drug is entrapped in the inner aqueous compartment [26] in dissolved form or in precipitated form." At no point, however, does Abra describe the cisplatin in the liposomes as precipitated. In fact, Abra expressly states that the cisplatin that was entrapped in the liposomes was in dissolved form, not solid (precipitated). See page 12, lines 7-12: "An aqueous solution of cisplatin (8.5 mg/ml cisplatin in 0.9% sodium chloride) was warmed. . . . The cisplatin solution and the lipid solution were added together to form liposomes" (emphases added). Abra states that the liposomes were cooled and the "final liposomes contained an internal phase of cisplatin encapsulated at a concentration of 8.5 mg/ml in 0.9% sodium chloride." Page 12, lines 17-18. That is, the internal phase of the liposomes was the "aqueous solution of cisplatin" that was used to form the liposomes.

Abra also describes the claimed step requiring selection of a liposome size that corresponds to liposomes having no precipitated compound. As noted above, Abra selected liposomes with a particle size of 100-120 nm (page 12, lines 13-14). ("The liposomes, following diafiltration and dialysis, were extruded through 0.2 μm and 0.1 μm polycarbonate filters to size the liposomes to between about 100-120 nm.") (Emphasis added.) Liposomes within the range of 100-120 nm are disclosed in Appellants'

specification (page 8, lines 13-14) as being a size suitable for maintaining supersaturated solutions. ("Typically, liposomes having a size of between 60-1,000 nm are suitable, preferably a size of between about 70-500 nm.")

Appellants' Example 1 (Specification, pages 22-24), which reads identically to Abra's Example 3 (pages 21-23), provides additional evidence that Abra selected liposomes of a size that does not contain precipitated compound. Specifically, Abra produced (page 12, lines 4-21) liposomes containing the same concentration of cisplatin present in liposomes prepared according to Appellants' Example 1, 8.5 mg/ml (Specification, page 24, lines 9-10). Abra used precisely the same steps used in Appellants' Example 1, and the resulting liposomes had a size range explicitly disclosed in Appellants' specification (page 8, lines 13-14) as being capable of maintaining a supersaturated solution without precipitation of the dissolved compound.

In our view these facts demonstrate, based on a preponderance of the evidence, that Abra selected liposomes of a size corresponding to liposomes having no precipitated compound therein. While Abra does not state that the selection was "based on said analyzing," as recited in claims 1 and 16, Abra performed a process step outwardly identical to that recited in claims. Therefore, in our view, Abra meets the claim limitation requiring the selection of liposomes having a size corresponding to liposomes having no entrapped precipitated compound.

Based on the evidence before us, it is reasonable to conclude that the 100-120 nm liposomes prepared as described on page 12 and Example 3 of Abra would not have contained precipitated cisplatin. As discussed above, the liposomes ranging in size from 100-120 nm disclosed by Abra at page 12 are within a size range disclosed in

the specification as being "preferably" used to entrap supersaturated drug solutions. Specification, page 8, lines 13-14 ("Typically, liposomes having a size of between 60-1,000 nm are suitable, preferably a size of between about 70-500 nm."). (Emphasis added.) As also discussed above, the liposomes disclosed at page 12 of Abra contain exactly the same concentration of entrapped cisplatin, 8.5 mg/ml in 0.9% sodium chloride, as is present in the liposomes prepared in Example 1 of Appellants' specification. Thus, because the liposomes described on page 12 of Abra are the same as the liposomes demonstrated by Appellants' own disclosure to contain dissolved rather than precipitated cisplatin, we conclude that the liposomes prepared as described on page 12 of Abra would not contain precipitated cisplatin.

To summarize, the fact that Appellants may have discovered an unrecognized result of an old process does not entitle them to claims to the old process. Despite Abra's failure to disclose the relationship between liposome size and the ability to maintain supersaturated solutions in the dissolved state under ambient conditions, based on the evidence before us, Abra in fact produced the same product recited in the claims, using the claimed process steps. Therefore, because a preponderance of the evidence supports the examiner's holding that the process steps and the product made by those steps are the same as disclosed in the prior art, we affirm the rejection.

Summary

Because Abra describes a process having all of the steps recited in claims 1 and 16, we find no error in the examiner's anticipation rejection. We therefore affirm the examiner's rejection of claims 1, 3-9, and 16, over Abra. The examiner also rejected

claims 1, 3-6, 8, 9, and 16 as anticipated by Yamamoto,[4] and rejected claim 7 as obvious in view of Yamamoto and Woodle.[5] Because Abra anticipates all pending claims, however, the rejection over Abra is dispositive of this appeal. We therefore find it unnecessary to reach the other grounds of rejection.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Donald E. Adams )
Administrative Patent Judge )
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Eric Grimes ) BOARD OF PATENT
Administrative Patent Judge ) APPEALS AND
)
) INTERFERENCES
)
Lora M. Green )
Administrative Patent Judge )

EG/FP/jlb

[4] Yamamoto et al., EP 0 551 169, published July 14, 1993
[5] Woodle et al., U.S. Patent 5,013,556, issued May 7, 1991

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